REMARKS

Claims 1-3, 5-9, 26 and 27 are pending in the application. Prior cancellation of claims 10-25 have been acknowledged to advance prosecution. Applicant reserves the right to prosecute claims 10-25 in a continuation or divisional application. Claims 1-3, 5-9, 26 and 27 were rejected. No claims were allowed.

Applicants again point out that their claim of foreign priority under 35 U.S.C § 119 has not yet been acknowledged by the Examiner. Applicants note that a certified copy India Patent Application No. 156/MAS/2003 was submitted to the Examiner on August 17, 2005, thereby completing the requirements for a claim of foreign priority under § 119. Applicants respectfully request that their claim of foreign priority be acknowledged in the next official communication.

Claims 1 and 6-9 have been amended to more clearly describe and distinctly claim the subject matter the Applicants consider their invention. In particular, claims 1 and 6-9 have been amended to replace the term "rabeprazole" with "2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfonyl]-1H-benzimidazole." Support for the amendments can be found throughout the specification as originally filed, *e.g.*, page 1, lines 4-5. No new matter has been introduced by these amendments.

Reconsideration and allowance of the finally rejected claims in view of the amendments above and the remarks below are respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 1-3, 5-9, 26 and 27 were rejected under 35 U.S.C. §§ 102(a), (b) and/or (e) as allegedly anticipated by Takashi et al. (JP 2001-39975) ("Takashi"), Souda et al. (U.S. Patent No. 5,045,552) ("Souda") and Reddy et al. (WO 03/082858) ("Reddy"). According to the Examiner, Takashi, Souda and Reddy specifically disclose the instant rabeprazole sodium salt. The term "Form Z," according to the Examiner, does not offer any demarcation of the claimed product from the prior art crystalline product. Applicants respectfully traverse this basis for rejection.

It has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Contrary to the

Examiner's position, Takashi, Souda and Reddy do not disclose the instant rabeprazole sodium salt with all its limitations. Claims 1-3, 5-9, 26 and 27 are directed to crystalline rabeprazole sodium Form Z having substantially the same X-ray powder diffraction ("XRPD") pattern as shown in Figure 1 of the instant specification, a pattern which is not expressly or inherently disclosed in the references cited by the Examiner.

As noted in Applicants' Appeal Brief submitted on September 27, 2006 ("Appeal Brief"), Souda describes in Example 33 a process for making rabeprazole sodium salt. There is no teaching or suggestion in Souda of crystalline rabeprazole sodium polymorphs, let alone the particular crystalline Form Z disclosed and claimed in the instant specification. Takashi appears to describe a crystal of rabeprazole salt:acetone complex having an XRPD pattern at page 5 substantially different from that shown in Figure 1 of the instant specification. Similarly, Reddy discloses Forms X and Y of rabeprazole sodium, each having XRPD patterns substantially different from that shown in Figure 1 of the instant specification. The differences in XRPD patterns between Takashi and Reddy on the one hand and the rabeprazole sodium Form Z on the other hand are clearly demonstrated by the data presented in Tables 1 (Takashi data), 2 (Reddy data) and 3 (Form Z data) of the instant specification. Applicants maintain that incorporating the XRPD pattern of Figure 1 into the claims adequately distinguishes the subject matter from the material disclosed in Takashi, Souda and Reddy.

According to the Examiner, these differences in XRPD patterns are not persuasive because Applicants have failed to provide a single crystal comparison of the instant compound and the prior art compounds at the same radiation parameters. The Examiner cites to Figure 4.21 of Bernstein, "Polymorphism in Molecular Crystals," p. 118 (2002) ("Bernstein") as showing the same compound having two different X-ray diffraction patterns. The examiner also cites to Davidovich et al., *Am. Phar. Rev.* 7:16 (2004) ("Davidovich") for the proposition that small changes in powder X-ray patterns can arise as experimental artifacts rather than polymorphism. Applicants submit that reliance on Bernstein and Davidovich is misplaced in this case.

First, the Examiner provides no support for the proposition that single crystal X-ray diffraction is the only way to demonstrate true polymorphism. In fact, the references of record clearly show that X-ray powder diffraction is the predominant tool to

characterize polymorphs. For example, Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, p. 235; "Brittain") states that:

> during the most common evaluation of drug substances, it is usually sufficient to establish only the polymorphic identity of the solid and to verify that the isolated compound is indeed of the desired structure. For these reasons, the technique of X-ray powder diffraction (XRPD) is the predominant tool for the study of polycrystalline material and is eminently suited for the routine characterization of polymorphs and solvates.

As such, U.S. Pharmacopia #23, 1995, pp. 1843-1844 ("USP #23") has established criteria for establishing identity of crystalline structures using XRPD analysis. With respect to single crystal X-ray diffraction, USP #23 states that "diffraction established for a single crystal can be used to support a specific powder pattern as being truly representative of a single phase." (p. 1843) (enphasis added.) Thus, USP #23 supports the use of single crystal X-ray diffraction for determining purity, not identity.

Second, although Figure 4.21 of Bernstein does show different X-ray diffraction patterns for sulphathiazole, this example is admittedly "dramatic" (p. 117.) More importantly, Fig. 4.21 does not compare two different powder diffraction patterns, but rather a powder diffraction pattern with an expected pattern calculated from the crystal structure. This explains the conclusion of Bernstein that "almost all of the expected diffraction peaks have been severely suppressed." (*Id.*) The Examiner has provided no evidence or reasoning why such peak suppression would be expected when comparing actual powder diffraction patterns between different rabeprazole sodium preparations.

Third, although Davidovich does state that changes in XRPD patterns can arise from experimental artifacts, such changes are said to be "small." (Abstract, p. 10.) An examination of Figures 2, 3, 5, 6 and 8-10 demonstrates just how small these changes are. In contrast, a comparison of the data presented in Tables 1 (Takashi data), 2 (Reddy data) and 3 (Form Z data) of the instant specification demonstrates quite large changes in XRPD patterns, even allowing for standard error in measurement.

Applicants submit that such large differences are simply not the type of minor variations contemplated by Davidovich as being due to XRPD artifacts rather than true polymorphism. That the instant crystalline rabeprazole sodium Form Z is indeed a

distinct polymorph from rabeprazole sodium Forms X and Y of Reddy is supported by their respective melting points: 224-230° C for the instant Form Z (*see* page 11, lines 21-22), and 140-150° for Form X and 160-170° C for Form Y of Reddy (*see* page 7, lines 8-9). *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Patent Application No. 08/732,254, now U.S. Patent No. 6,452,007 (BPAI 2001) ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency.").

Accordingly, Applicants submit that claims 1-3, 5-9, 26 and 27 are not anticipated by Takashi, Souda or Reddy, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-3, 5-9, 26 and 27 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the combined teachings of Takashi, Souda and Nochi (*Chem. Pharm. Bull.* 44(10) 1853-1857 (1996)) ("Nochi") in view of Haleblian et al. (*J. Pharm. Sciences*, (1969), 58 pp. 911-929) ("Haleblian"), Brittain, Muzaffar et al. (*J. of Pharmacy* (Lahore) 1979, 1(1), 59-66) ("Muzaffer"), Jain et al. (*Indian Drugs*, 1986, 23 (6) 315-329) ("Jain"), Chemical & Engineering News, Feb. 2003 ("C&E News"), USP #23 and Concise Encyclopedia Chemistry, pages 872-873 (1993) ("CEC"). According to the Examiner, Takashi, Souda and Reddy teach the crystalline form of rabeprazole and rabeprazole sodium, as well as pharmaceutical compositions. Further, according to the Examiner, Brittain, Halbein, Muzaffar and Jain teach that compounds can exist in different crystalline forms, while C&E News, USP #23 and CEC teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Thus, according to the Examiner, it would appear obvious to one skilled in the art that the instant compound would exist in different polymorphic forms. Applicants respectfully traverse this basis for rejection.

The standards for making an obviousness rejection are summarized in MPEP § 706.02(j) as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above with respect to the § 102 rejection, there is no teaching or suggestion in Takashi or Souda of the instantly claimed crystalline rabeprazole sodium Form Z. Nochi, on the other hand, describes at page 1853 X-ray crystallographic analyses of a synthetic intermediate of rabeprazole sodium (benzyloxymethylated rabeprazole sodium). Nochi explains in the Experimental Section that rabeprazole sodium was prepared according to the method described in Souda, but that "E3810 (rabeprazole sodium) could hardly be crystallized," casting doubt on the likelihood that Souda discloses a crystalline rabeprazole sodium. Thus, none of the references, alone or in combination, teach or suggest crystalline rabeprazole sodium Form Z having substantially the same X-ray powder diffraction pattern as shown in Figure 1 of the instant specification. This alone is enough to overcome the Examiner's obviousness rejection. *See Ex parte Havens*, *supra* ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added). The ancillary references cited by the Examiner merely provide general background information relating to the study and preparation of polymorphs or case histories of specific polymorphic compounds (none of which is rabeprazole sodium), and thus add nothing over the primary references.

As noted in Applicants' Appeal Brief, the proper test for obviousness in this case is not whether the existence of amorphous compounds is suggested by the prior art, but

whether it would have been obvious to make the particular rabeprazole sodium Form Z claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. Thee correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, (Fed. Cir. 1989) (unpublished decision) (emphasis added).

Here, the references cited by the Examiner suggest at most the possible existence of other solid state forms of rabeprazole sodium. The Examiner has pointed to nothing in the cited references, however, that would suggest to one skilled in the art the particular rabeprazole sodium Form Z claimed in the instant application, or a method for its preparation. In fact, as noted by Applicants in their Appeal Brief, CEC (p. 32) states that "no method yet exists to predict the polymorphs of a solid compound with significant certainty." The Examiner admits as much by quoting the CEC passage under the enablement rejection at page 8 of instant Office Action (discussed *infra*). Because of this uncertainty, Applicants maintain that no *prima facie* case for obviousness of claims 1-3, 5-9, 26 and 27 under § 103(a) has been made out by the Examiner. *See Ex parte Andrews*, Appeal No. 2002-0941 for U.S. Patent Application No. 09/166,445, now U.S. Patent No. 6,713,481 (BPAI 2003) ("[T]he examiner has not adequately explained how a person having ordinary skill would have been led from 'here to there,' i.e., from the [prior art] compound having formula I to the crystalline polymorph form I recited in claims 1 through 5."); *Ex parte Portmann*, Appeal No. 2003-1199 for U.S. Patent Application No. 09/125,329, now U.S. Patent No. 6,740,669 (BPAI 2004) (same).

As was done in the previous Office Action, the Examiner contends that:

> [A]s set forth by the court in In re Cofer 148 USPQ 268, Ex parte Hartop 139 USPQ 5252, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained thereform, are unpatentable. The instant claims are drawn to the ***same***

> ***pure substance*** as the prior art that only having *different arrangements and or different conformations of the molecule*. A mere difference in physical property is a well known conventional variation for the same pure substance is prima facie obvious. (Emphasis in original.)

The Examiner still appears to be taking the position that new solid state forms are *per se* unpatentable over the originally identified compound or previously identified solid state forms of the same compound. Such a rule, however, is inconsistent with the law on obviousness. *See Ex parte Andrews*, *supra* (quoting *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995) ("The use of *per se* rules flouts § 103 and the fundamental case law applying it. . . [R]eliance on *per se* rules of obviousness is legally incorrect and must cease.").

Applicants maintain that the Examiner's reliance on *In re Cofer* and *Ex parte Hartop* is misplaced in this case. *In re Cofer* actually held the claimed 2,2-bis form of a compound to be patentable because

> [T]he board failed to address . . . whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining the structure or form. (Emphasis added.)

354 F.2d 664, 668 (CCPA 1966).

The *Cofer* court addressed the *Ex parte Hartop* decision, which had been relied upon by the board in finding the claimed 2,2-bis form unpatentable:

> We think examination of the decisions relied on . . . in *Hartop* will demonstrate that the materials involved therein were found unpatentable where the alleged difference in form or purity of those substances was either disclosed or inherent therein. (Emphasis added.)

Id. at 667.

Here, as discussed above, the references cited by the Examiner neither disclose or suggest the particular solid form disclosed and claimed in the instant application.

As Applicants noted in their Appeal Brief, the Board of Patent *Appeals* & Interferences has recently cautioned against the reliance on *Ex parte Hartop* in polymorph cases. As stated in *Ex parte Gala*:

> The examiner relies heavily on this proposition of law set forth in *Ex parte Hartop* . . . : "[m]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable." According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable. We disagree. Here, we invite attention to *In re Cofer* . . . , where the court substantially discredited PTO reliance on the above-quoted proposition of law in *Hartop*. Like the situation presented in *Cofer*, the examiner in this case has not adequately established that the prior art (1) suggests the polymorph form 2 of loratadine; or (2) discloses or renders obvious a method for making the polymorph form 2 of loratadine. (Emphasis added.)

Appeal No. 2001-0987 for U.S. Patent Application No. 09/169,109, now U.S. Patent No. 6,335,347 (BPAI 2001); *see also Ex parte Andrews*, *supra* ("[T]he principal of law enunciated in *Ex parte Hartop* . . . has been substantially discredited in *In re Cofer* . . .").

According to the Examiner, Applicants have failed to show advantage for the instant polymorphs and compositions. The Examiner also states that Applicants' assertion in their Appeal Brief that the USPTO routinely issues patents to new solid state forms is not persuasive. The Examiner points to page 185 of Brittain, which states that "[i]n 1990 Byrn and Pfeiffer found that more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, etc."

First, Applicants note that the cited Brittain passage supports their assertion that the USPTO routinely issues patents directed to new polymorphs, thus indicating that they are patentable subject matter. In addition, the endnote for the passage states that its content was personally communicated to Brittain by Bryn in 1996. There is no discussion in Brittain of the subject matter of the patents, the prior art of record (if any), the bases for rejections (if any) or the effect of the purported advantages on allowance (if any).

In any event, Applicants respectfully submit that unexpected properties need not be demonstrated in this case because a *prima facie* case of obviousness has not been made under the proper test described above. The CCPA in *In re Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unexpected properties, when analyzing the patentability of new solid state forms:

> No reason exists for applying the law relating to structural obviousness of those compounds which are homologs or isomers of each other to this case. . . . A zeolite, like those of the instant case, is not a compound which is a homolog or isomer of another, but is a mixture of various compounds related to each other by a particular crystal structure. Moreover, no other chemical theory has been cited as a basis for considering appellants' zeolite as prima facie obvious in view of [the prior art] zeolite R.

592 F.2d 1161, 1167-68 (CCPA 1979).

Accordingly, Applicants submit claims 1-3, 5-9, 26 and 27 are not unpatentable over Takashi, Souda and Nochi in view of Haleblian, Brittain, Muzaffar, Jain, C&E News, USP #23 and CEC, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 112

(a) Claims 6-9 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. According to the Examiner, there is a lack of description as to whether the compositions are able to maintain the compounds in the crystalline form claimed, and the specification lacks direction or guidance for maintaining the compounds in the crystalline form claimed. Applicants respectfully traverse this basis for rejection.

Contrary to the Examiner's characterization, claims 6-9 are not directed to compositions, but rather to rabeprazole sodium as a solid. Although Applicants' Amendment After Final submitted on August 7, 2006, attempted to amend claims 6-9 to recite compositions, the Advisory Action mailed on August 11, 2006, indicated that the proposed amendments would not be entered. As such, the claims as presented by Applicants in their Amendment and Response submitted on February 17, 2006

(containing claims 6-9 in the same format as presented herein), remain pending for examination.

Because claims 6-9 recite crystalline rabeprazole sodium Form Z, the XRPD pattern for which is shown in Figure 1, Applicants submit that claims 6-9 are adequately described and enabled, and reconsideration of this basis for rejection is respectfully requested.

(b) Claims 1 and 6-9 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Examiner, "Form Z" is not a universal identification of compounds, and "rabeprazole sodium" is not defined in the claim. Applicants respectfully traverse this basis for rejection.

Regarding the term "Form Z," claims 1 and 6-9 specifically recite "having substantially the same X-ray diffraction pattern as shown in Figure 1," which Applicants submit adequately defines the metes and bounds of the claimed subject matter. Reconsideration of this basis for rejection is respectfully requested.

Regarding the term "rabeprazole," as explained in Applicants' Appeal Brief, rabeprazole is not a trademark or tradename, but rather the USAN adopted name accepted by the FDA as the official name for 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfonyl]-1H-benzimidazole. As such, the term is not indefinite. However, solely in the interest of expediting prosecution, claims 1 and 6-9 have been amended to replace "rabeprazole" with "2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfonyl]-1H-benzimidazole." Reconsideration of this basis for rejection is respectfully requested.

Claim Objections

Claim 6 was objected to, as allegedly containing a misspelling of the term "solid" in line 3. Applicants respectfully traverse this basis for rejection.

Contrary to the Examiner's contention, claim 6 does not contain a misspelling of the term "solid" in line 3. Although Applicants' Amendment After Final submitted on August 7, 2006, contained a misspelling of solid in claim 6, the Advisory Action mailed on August 11, 2006, indicated that the proposed amendments would not be entered. As

such, the claims as presented by Applicants in their Amendment and Response submitted on February 17, 2006 (containing claim 6 with no misspelling), remain pending for examination. Accordingly, reconsideration of this basis for objection is respectfully requested.

Double Patenting

Claims 1-3, 5-9, 26 and 27 were provisionally rejected under the judicially created doctrine of obviousness-type patenting as allegedly obvious over claims 1-3, 5-9, 11-13, 26 and 27 of copending U.S. Patent Application No. 10/505,826 ("the '826 application") in view of Halbein, Muzaffar, Jain, C&E News, USP, Brittain and CEC. According to the Examiner, the '826 application discloses crystal forms of the instant salts and corresponding compositions, and the ancillary references teach that mere existence of further polymorphs is not in itself regarded as unexpected.

According to MPEP § 804:

> A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

As noted in Applicants' Appeal Brief, the claims of the '826 application are directed to crystalline Forms X and Y of rabeprazole sodium having X-ray powder diffraction patterns substantially different from that of the instantly claimed Form Z. As with the obviousness rejection discussed above, the Examiner points to nothing in the claims of the '826 application or the cited ancillary references that would suggest to one skilled in the art the particular rabeprazole sodium Form Z claimed in the instant application, or a method for its preparation. *See Ex parte Andrews*, *supra* ("As discussed above, the examiner has pointed to nothing in either claims or the disclosure of the [commonly assigned] patent that would have suggested the S and T crystal forms of delavirdine mesylate to a person of ordinary skill in the art. We therefore reverse the

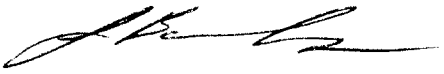
rejection for obviousness-type double patenting."); *Ex parte Portmann*, *supra* ("The claims of the issued patent recite crystal modifications B and C of [the compound], which are patentably distinct from crystal modifications A and A' recited in the claims before us.").

Accordingly, Applicants submit that claims 1-3, 5-9, 26 and 27 are not invalid for obviousness-type double patenting, and reconsideration of this basis for rejection is respectfully requested.

CONCLUSION

It is believed that claims 1-3, 5-9, 26 and 27 are in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number indicated below to discuss the same.

Respectfully submitted,



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